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Dockets Management Branch
Division Management Systems and Policy
Office of Human Resources
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061 (HFA-305)
Rockville, MD 20852

RE: Docket Number 98D-1232, Comments on *Points to Consider Guidance Document on Assayed and Unassayed Control Material*

To whom it may concern,

For and on behalf of Bio-Rad Laboratories, we are hereby submitting comments to the Food and Drug Administration on Docket Number 98D-1232, *Points to Consider Guidance Document on Assayed and Unassayed Control Material.*

Bio-Rad Laboratories is the world's largest manufacturer of *in vitro* diagnostic third party multianalyte quality control materials and is the largest supplier of OEM control products. Bio-Rad currently manufactures over 90 multianalyte quality controls.

The quality control products manufactured by Bio-Rad are generally considered "third party" quality controls. Third party quality controls are preferred by our customers since they allow an independent unbiased assessment of the diagnostic test methods and systems used in their laboratories which are purchased from other diagnostic manufacturers.

In addition, most of these "third party" quality controls produced by Bio-Rad contain multiple analytes. Multianalyte controls are preferred by customers since they reduce the substantial cost of having numerous single analyte controls, allow "one stop" shopping for these customers and better simulate patient samples.

Bio-Rad has an overall 98% customer satisfaction rating based upon our 1998 survey.

Since the Medical Device Amendments were enacted in 1976, Bio-Rad Laboratories has obtained premarket clearance for 116 quality control materials. We have also successfully updated premarket clearance files in 17 additional information submissions.

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In December of 1997, Bio-Rad Laboratories acquired the quality controls business of Chiron Diagnostics. Premarket clearance has been successfully received for 45 quality control materials through Chiron and the progenitor owners of this business.

Bio-Rad Laboratories is basing our comments regarding this draft guidance document on both our long standing successful relationship with the Food and Drug Administration and on the expertise from our current marketplace position in the quality controls industry.

We applaud the Food and Drug Administration for moving forward and preparing this guideline. However, we are deeply concerned with the substantial impact to the quality controls business and the potential loss of the current value and availability of unbiased third party assessment controls to the clinical laboratory if this guideline is enacted in its current form.

This guideline has the potential to force some third party control manufacturers out of the industry. Third party control manufacturers that are able to stay in business will be forced to substantially reduce method listings on their package inserts. Costs will then need to be increased to customers that would purchase products for the remaining methods. Customers will then be forced to use the subjective and dependent quality control materials supplied by test method manufacturers. These quality controls are generally multiple single analyte controls that are not only cost prohibitive but can also be biased to the manufacturers test methods and may not be reflective of patient performance.

The Food and Drug Administration needs to measure the cost to laboratories if these guidelines are implemented and compare them to the cost of the true value realized by the laboratory.

We feel that several components of this draft guidance document defy the spirit of the FDA Modernization Act of 1997 by actually increasing the standards by which quality control materials are introduced in the marketplace. In addition, this guideline actually exceeds the current practice at the FDA for review of premarket notification submissions for quality control materials.

Representatives from Bio-Rad Laboratories are available to meet with you in person, by conference call or in a public hearing to partner with the Food and Drug Administration to draft a guideline that is in the best interest of public health, industry and meets statutory requirements.

Please contact me to schedule a meeting or if you require any additional information on these comments at (949)598-1285.

Respectfully,

Elizabeth Platt

Elizabeth Platt
Regulatory Affairs Supervisor
Bio-Rad Laboratories, Irvine Facility

Comments from Bio-Rad Laboratories on *Points to Consider Guidance Document on Assayed and Unassayed Control Material,* Docket Number 98D-1232

For your convenience, the comments on this proposed guideline are presented in the same order as they appear in the draft document. Citations from the proposed guideline are italicized to distinguish them from the comments of Bio-Rad Laboratories.

I. *Device Description*

Assayed QC materials have analyte values assigned to them by the manufacturer using appropriate analytical methods or procedures. Target quantitative ranges or qualitative values, e.g., positive or negative, are presented in the product labeling with stated tolerances for specific system applications.

This section indicates that assayed quality control materials list "target" ranges in the package inserts. This is a limiting statement. Manufacturers may list manufacturing targets, mean assigned values for methods or acceptable ranges for methods or a combination of these.

In addition, the Agency refers to listing of *stated tolerances for specific system applications.* The ranges that most manufacturers list are not considered stated tolerances for systems and applications, however they are considered acceptable ranges to be used only as a guide that and are based upon calculations and not on system tolerances.

System tolerances are actually out of the realm of the control of third party quality control manufacturers. These tolerances are only under the control of the test method/system manufacturer and the testing laboratory.

Under the requirements of the Clinical Laboratory Improvement Amendments of 1988 (CLIA), the laboratory must establish their own statistical parameters for quality control materials in their individual laboratories for each lot through repetitive testing. A laboratory actually assigns their own acceptable ranges for the quality control material for use in their laboratory based on multiple analysis and statistical calculations.

Under the guidelines of the National Committee for Clinical Laboratory Standards (NCCLS), the values listed on assayed quality control inserts are to be used only as guides, and actual values for the means and standard deviations must be established through replicate testing in the laboratory.

We are requesting that the verbiage on *target ranges* be expanded to include manufacturing targets, mean assigned values for methods, acceptable ranges for methods or the option of a combination of these. We are requesting that *stated tolerances for specific system applications* be removed from this section.

II. *Intended Use*

A QC material is intended to monitor and evaluate the precision and accuracy of a test system by assessing the analytical performance of the In Vitro Diagnostic (IVD) Device. It is used to detect and estimate inaccuracy (the difference between the average values obtained when a sample is repeatedly tested and the true

value) and imprecision (the extent to which results obtained when testing repeatedly agree with each other) resulting from reagent or instrument defects, or operator variation. QC material may be used for internal and/or external laboratory QC programs.

Under the recommendation of an FDA reviewer in 1995, Bio-Rad Laboratories removed "accuracy" from the intended use template for of all of our quality control products. We make no claims that our products are intended to measure "accuracy" or trueness to the actual values.

"Accuracy" controls are completely separate from "precision controls" and are a European contrivance that supports a cottage industry of reference laboratories located primarily in Germany. Accuracy controls should only be used for calibration verification or for proficiency testing.

Proposed international standards are exempting control products that are not intended to demonstrate trueness of measurement from requirements for metrological traceability of assigned values *(ISO/CD 17511: Measurement of quantities in samples of biological origin – Metrological traceability of values assigned to calibrators and control materials*).

We question the value, practicality, economic impact and the logic of mandating accuracy controls for daily use. The average cost to assign "accurate" values per analyte is well into the five-figure range, and the values that are provided are only specific to a single reference method for each analyte. Since test methods values in the United States are not required to be equivalent to the values obtained using reference methods, this could add an unnecessary cost of millions of dollars to each multianalyte quality control lot produced by manufacturers. This would have limited or no value to the customer and in return, only increase product costs.

In general, quality control materials are typically used only to measure imprecision and to monitor relative performance within a specified group. These products provide the laboratory a tool to gauge the daily reliability of their analytical processes.

We strongly oppose this section of the draft guideline and are requesting that references to *accuracy* controls and use of these controls *to assess the trueness of values* in the *Intended Use* section be removed.

III. Preclinical Data for Submissions

A. For preclinical data:

1) The manufacturer should provide a summary description of how the control material is prepared during manufacturing.

Most quality control materials are considered Class I, Tier 1 devices and undergo only a labeling review.

We oppose providing descriptions of manufacturing processes. We have never been required to provide this information to obtain 510(k) approval.

We feel this information is not necessary to demonstrate substantial equivalence.

We are requesting either removal of this requirement or the inclusion of this requirement for Class II devices only. If the requirement were applied to Class II

devices, we would request additional information in the guideline on the appropriate content of this section.

2) Information on the source, i.e., human or animal species, synthetic or recombinant analyte or metabolite, organism (strain or portion of an organism if appropriate), nucleic acid segment, and specific nucleic acid sequence should be included.

Most quality control materials are considered Class I, Tier 1 devices and undergo only a labeling review.

We oppose providing specific descriptions on raw material sources for each analyte in 510(k) submissions. We generally have not been required to provide this information to obtain 510(k) approval for quality control materials.

We feel this information is not necessary to demonstrate substantial equivalence.

We are also concerned about the general value of this information to the Agency.

Bio-Rad Laboratories is requesting removal of this requirement.

3) Additionally, the matrix (or material in which the substance is found e.g. blood, urine), should be identified and the composition and characteristics of all components, stabilizers and preservatives, or clarifiers should be described. Information should be provided on the volumes, concentrations, and particle sizes of the QC materials.

Composition and characteristics of all components, stabilizers and preservatives has never been required for 510(k) approval before. This is proprietary information and is not required to demonstrate substantial equivalence.

In addition, we consider providing volumes, particle size and concentrations of QC materials in the same category and should not be required to demonstrate substantial equivalence.

For multi-analyte controls, this listing would be volumes long and is an undue burden on manufactures to provide this information. This is basically asking the manufacturer to provide formulation to obtain premarket clearance.

We are also concerned about the general value of this information to the Agency and the criteria and consistency that will be applied during review.

We are requesting complete removal of the requirement to identify *composition and characteristics of all components, stabilizers and preservatives, or clarifiers should be described.* We are also requesting removal of the requirement to provide information *on the volumes, concentrations, and particle sizes of the QC materials.*

B. For assayed QC material, the protocol that was followed during the range or value determination process should be provided.
A description of the analytical methods, materials used, specific system applications, the number of replicates, runs and instruments, and the statistical analyses by which the range was established should be included.

We generally describe how values are assigned in 510(k) submissions for quality control materials and include samples of the protocol letters and data report forms that we send to manufacturers and reference laboratories.

However, detailed descriptions of the analytical methods, materials used, specific system applications, the number of replicates, runs and instruments, and the statistical analyses by which the range was established have not been required to obtain 510(k) approval.

We feel this information is not necessary to demonstrate substantial equivalence.

The multianalyte controls manufactured by Bio-Rad contain up to 91 analytes and list up to 1100 different methods. It is therefore not reasonable to include this information in the 510(k) submission for every analyte and every method. The submissions would be verbose. A general summary should be able to be used for this case.

We are also concerned about the general value of this information to the Agency and the criteria and consistency that will be applied during its review.

We are requesting that the FDA continue to proceed under current practice and allow manufactures to continue to use current summary descriptions for assignment of values.

D. The effect of the sample itself on the test results of various analytes in a human source QC material may differ from a non-human source and may require evaluation. This is dependent upon the amount of information known about the non-human source and how well its performance is understood. One suggested procedure is to add a known amount of the substance or analyte to be determined or measured (spiking) to a minimum of 5 samples each of the proposed matrix (e.g. non human blood or serum) and the matrix the QC is intended to monitor (e.g.; human blood) with equal analyte concentrations which span the clinically relevant range. This should be performed for each analyte on a number of methods consistent with the intended use and the "uniqueness" of the matrix. The performance of control material prepared in the proposed matrix and those prepared in the human matrix should be evaluated for the presence and concentration of each analyte. Plotting the two sets of values and performing a linear regression analysis may provide the bias of each method. Alternately bias may be evaluated by recovery studies spanning the concentrations claimed and employing all relevant analytical methods. A description of the procedure or protocol used to characterize the bias measurement should be provided.

Determination of matrix bias for non-human sourced controls has not previously been required by the Agency to obtain 510(k) approval for these types of quality control products.

We feel this information is not necessary to demonstrate substantial equivalence.

The first testing recommendation provided by the agency in this guideline would actually require parallel development of two products for this comparison testing, one containing all of the analytes in a human based product and the other containing the same analytes in the non-human sourced base. This testing recommendation is therefore not reasonable and would result in a substantial increase in overall development costs that may even preclude manufacturers from producing these controls.

The second testing recommendation provided by the agency in this guideline requires that the evaluation be conducted through recovery studies that span the concentrations claimed and employ all relevant analytical methods.

The multianalyte controls manufactured by Bio-Rad contain up to 91 analytes and list up to 1100 different methods. The cost to perform this type of testing for this quantity of methods and analytes would be exorbitant. We would be forced to reduce the method listings in the package inserts for these products.

Many customers actually prefer to use these non-human sourced products due to the general lower costs of the materials and the absence of the risks associated with the handling of human sourced products. Enactment of this requirement will ultimately reduce the availably of these products to laboratories.

We are requesting that the FDA continue to proceed under current practice and remove this requirement from the guideline.

E. For assayed QC material, the levels of each constituent, and the acceptable range of the level should be furnished. The statistical parameters of coefficients of variation, standard deviations, and confidence intervals should be presented.

It is not necessary to provide concentrations and specifications for each analyte to obtain (510)k approval. This information is not necessary to demonstrate substantial equivalence and has never been required.

Use of statistical parameters of coefficients of variation, standard deviations, and confidence intervals are generally used in the manufacture of test methods and are not applied to the quality controls manufacturing processes.

We are also concerned about the general value of this information to the Agency and the criteria and consistency that will be applied during review.

We are requesting complete removal of this requirement from the guidance document.

F. When a QC material is unusual and/or significantly different in composition from the analyte it is intended to monitor, the manufacturer should perform a series of tests on actual clinical samples run in parallel with the QC material. This will verify that the QC material is as sensitive as actual patient samples to all anticipated analytical variable inherent to the assay system. These may include variables such as temperature variations, reagent deterioration, or pipetting or sample transfer errors. This testing assures that the same factors which affect a patient diagnostic test result would have a similar affect on the quality control result, and could, thereby, alert the user to potential problems.

This information is not necessary to demonstrate substantial equivalence and has never been required to obtain 510(k) approval.

We strongly object to the requirement for manufacturers to parallel test quality control materials with actual clinical samples.

Our role as a manufacturer is different from that of the clinical laboratory environment where a sample is assayed only for specific tests ordered by a patient's physician. In the manufacturing environment, samples may be assayed for analytes without the discretion of a physician, including testing for infectious disease markers. We are very concerned about the legal issues surrounding

patient confidentiality and informed consent. Since these patient samples would be used in the manufacturing environment, we are also concerned about the requirements for compensation of the patients for use of their samples.

In addition, it is not the role of the quality control material to detect all anticipated analytical variances inherent to assay systems. This is the responsibility of the test method manufacturer. This reverts back to the fundamental basic concept of the intended use of quality control materials.

The human factors for quality control materials referenced in this requirement are generally addressed instead through validation testing in the clinical laboratory setting, and not through parallel testing by the manufacturer with patient samples.

We are requesting that the FDA continue to proceed under current practice and remove this requirement from the guideline.

SPECIAL CONSIDERATIONS:

A. *The concentrations of QC materials should be formulated such that levels of the substances or factors to be detected or measured in samples from patients span the medical decision range of the assay and should ideally target medically relevant decision points (those which result in a change of treatment). If the concentration does not stress the medical decision point of the assay, then a warning should be included in the labeling stating that the QC material is only intended to monitor for gross systematic errors.*

It is impossible for a multianlayte quality control material that lists multiple methods to challenge the decision point for every assay for each analyte listed on the inserts. There is too much variation between values from method to method.

The multianalyte controls manufactured by Bio-Rad contain up to 91 analytes and list up to 1100 different methods.

You would have to have one control for every test kit and each analyte on the market to meet this requirement.

This would all but eliminate third party control manufacturers from the market.

In addition, the actual use of quality control materials in the laboratory is under the providence of the Health Care Financing Administration (HCFA) and has been duly delegated by HCFA to be under the control of the Medical Director of the laboratory and is not up to Device Manufacturers.

Current trends in the industry are actually to choose quality control materials to challenge the actual assay range and not the medical decision points of these assays.

The added requirement in this draft guideline to list a warning if the medical decision points are not challenged by the quality control indicating the product *is only intended to monitor for gross systematic errors* is unreasonable and will not be accepted by our customers. This reverts back to the fundamental basic concept of the intended use of quality control materials.

We are requesting complete removal of this requirement from the guidance document.

VII. Labeling Information

A. Intended Use:

If the concentration does not challenge the medical decision point of the assay, a warning should be included in the labeling stating that the control is only intended to monitor for gross systematic errors.

Once again, it is not possible to challenge the decision point for every method listed on an insert for a quality control material for multiple methods.

It is therefore unreasonable to put warnings on products indicating that they are only intended to monitor for gross systematic errors.

We are requesting complete removal of this requirement from the guidance document.

B. Reagents:

The following information should be provided in the description: the source of components (i.e., from human or animal species, synthetic, or purified chemicals); whether recombinant nucleic acid from an microorganism, or an entire microorganism (ATCC strain or portion of a microorganism); media or cell line used for culture; human donor characterization; nucleic acid segment and specific nucleic acid sequence; the matrix; a list of all stabilizers, preservatives, or clarifiers contained in the control mixture; volumes used ; concentrations used; particle sizes; and inactivation methods.

Manufacturers have never been required by FDA reviewers during the submission process to list each specific stabilizer and preservative in the labeling for quality control products. We have only been required to list their presence if the preservative is sodium azide in excess of 0.1% due to the regulatory requirements for listing of hazardous substances and to protect the laboratorian.

Preservatives and stabilizers are the most proprietary ingredients in the quality control formulation and should not be required to be listed by name. This information is not necessary for the customer.

We are requesting that the FDA continue to proceed under current practice and not require manufacturers to list each specific stabilizer and preservative in the labeling for quality control products with the exception of hazardous substances including sodium azide concentrations exceeding 0.1%.

F. Expected values, as appropriate.

The labeling for assayed QC materials should provide the established expected value(s) for the control(s), along with ranges, standard deviations, coefficients of variation, confidence intervals, and methods applications, as appropriate.

Assigned values should be identified for each constituent and level. This may be furnished as an attachment to the labeling.

For assayed materials, the protocol used to establish the acceptable value and/or range for the QC material, e.g., low, mid or high level, should be provided. The analytical methods, number of testing replications, test runs and

instruments, and the statistical analyses by which the values and/or range was established should be described.

Manufacturers generally describe how values are assigned in the package insert. The multianalyte controls manufactured by Bio-Rad contain up to 91 analytes and list up to 1100 different methods. It is therefore not reasonable to list the number of replicates, test runs and statistical analysis for every analyte and every method. The package insert would be too lengthy. A general summary should be able to be used for this case.

We are requesting that the FDA continue to proceed under current practice and allow manufactures to continue to use current descriptions for assignment of values.

G. *Performance characteristics, as appropriate.*

Any significant matrix bias should be described along with a brief description of how the bias was determined.

Description of matrix bias and their determinations provides no relevant information to the end user and is therefore not a reasonable requirement.

As we indicated previously in these comments, we strongly oppose the requirements for evaluation of matrix bias for non-human sourced controls contained within this draft guideline.

Even if the matrix bias was determined for every analyte and test method using the requirements in this draft guideline for multianalyte non-human sourced control materials, listing of the descriptions and results of bias testing would substantially impact the size of package inserts.

We are requesting that the FDA continue to proceed under current practice and remove this requirement from the guideline.

The ability or sensitivity of the QC material to detect known analytical problems should be defined.

As we have indicated throughout these comments, it is not the role of quality control materials to detect known analytical problems. This is the responsibility of the test method manufacturer. This reverts back to the fundamental basic concept of the intended use of quality control materials.

Quality control materials are typically used to only to measure imprecision and to monitor relative performance within a specified group. These products provide the laboratory a tool to gauge the daily reliability of their analytical processes.

We are requesting that the FDA continue to proceed under current practice and remove this requirement from the guideline.

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